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Hepatitis C virus infection

B. J. Thomson and R. G. Finch

Department of Infectious Diseases, University of Nottingham, Nottingham, UK

ABSTRACT

Hepatitis C virus (HCV) infection is a major public health problem. Up to 3% of the world's population is infected with HCV, and at least 200 000 adults in the UK carry the virus. Of those exposed to HCV, 80% become chronically infected, and at least 30% of carriers develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. This review provides an overview of selected features of the molecular biology and pathogenesis of HCV infection, and thereafter discusses in detail the epidemiology of HCV, the hepatic and extra-hepatic diseases caused by the virus, and the current treatment options for both acute and chronic virus infection. The special cases of healthcare workers, prison inmates and individuals coinfected with human immunodeficiency virus and HCV are considered in detail.

Keywords Epidemiology, extra-hepatic disease, hepatitis C virus, liver disease, treatment

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INTRODUCTION

Hepatitis C virus (HCV) is a major global healthcare problem. The WHO estimates that up to 3% of the world's population has been infected with the virus, equating to more than 170 million carriers of HCV worldwide. Within this broad estimate, there is considerable variability in the prevalence of infection [1]. The seroprevalence of HCV in the USA is 1.8% in an unselected adult population [2], whereas rates of up to 25% have been reported in Egypt. In the UK, it is estimated that at least 200 000 adults carry the virus, most of whom are unaware of their infection [3]. Of those individuals exposed to HCV, 80% become persistently infected, and up to 30% of these develop progressive liver disease, including cirrhosis and hepatocellular carcinoma (HCC) [4,5]. Indeed, HCV infection is now the leading reason for liver transplantation [6]. Therefore, HCV is already a major challenge to healthcare services throughout the world, and is likely to become an even greater burden during the next two decades. In recognition of the importance of this epidemic, the UK Department of Health recently produced a 'Hepatitis C Strategy for England', with the aims of identifying those individuals who are chronically infected, and providing specialist advice and treatment via coordinated pathways of patient care [3].

Corresponding author and reprint requests: B. J. Thomson, Department of Infectious Diseases, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB, UK
E-mail: brian.thomson@nottingham.ac.uk

THE VIRUS

HCV is a small, enveloped RNA virus which has been allocated to a unique genus, designated *Hepacivirus*, within the family Flaviridae. The molecular biology of the virus has been reviewed previously [7]. The HCV genome is a single-stranded RNA molecule of positive polarity that contains a single open reading frame with the potential to encode a protein of *c*. 3000 amino-acids in length. This open reading frame is flanked by 5′ and 3′ non-coding regions, each of which contains conserved RNA structures essential for the translation of virus protein and genome replication. The HCV precursor protein is processed by host-cell and virus proteases to yield ten structural and non-structural (NS) proteins (Fig. 1). The structural components of the virion are the core protein and envelope glycoproteins, E1 and E2. These proteins are cleaved from the precursor by host-cell peptidases.

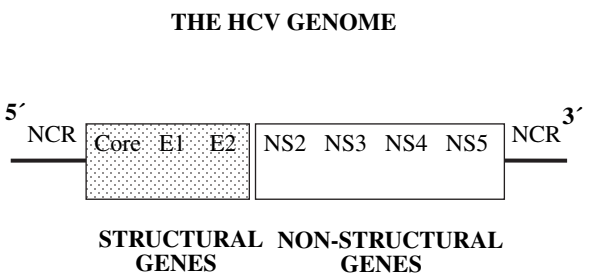

Fig. 1. The structure of the hepatitis C virus genome [7]. The 5′ non-coding region (NCR) contains four highly conserved RNA domains and an internal ribosome entry site. Structural proteins include core, which forms the virus capsid, and the envelope glycoproteins E1 and E2. The structural proteins are separated from the non-structural (NS) proteins by a short peptide, P7 (not shown). NS proteins are designated NS2 to NS5. NS4 and NS5 are each processed further into two subunits, A and B. NS2 is a component of the NS2–NS3 metalloprotease that autocatalyses cleavage of the NS2–NS3 junction; NS3 contributes to the NS2–NS3 protease and contains a separate serine protease that acts with co-factor NS4A to release the remaining NS proteins. The C-terminal region of NS3 contains an RNA helicase and nucleotide triphosphatase activity required for virus replication. NS5B is the RNA-dependent RNA polymerase. The functions of NS4B and NS5A in the virus life-cycle are unknown. The 3′-NCR contains a series of stable RNA stem–loop structures and a polypyrimidine tract that is essential for genome replication.

The NS proteins, designated NS2 to NS5B, are involved in the further processing of the precursor polypeptide and virus replication. The structure of the HCV genome and the function of individual proteins are described in detail in Fig. 1.

In common with other RNA-dependent polymerases, the HCV RNA polymerase (NS5B) does not have a proof-reading capability, and therefore generates considerable genetic diversity. HCV is divided into six genotypes, which differ from each other by up to 30% in nucleotide sequence, and a large and growing number of subtypes [7]. There is no consistent evidence that the genotype affects the outcome of HCV infection. In contrast, response to therapy clearly correlates with genotype. In addition to clustering into major and minor genotypes, HCV evolves within individuals as a 'quasi-species' of closely related but distinct genetic variants. The role of quasi-species in the pathogenesis of disease remains controversial, but it is likely that, as with human immunodeficiency virus (HIV), the capacity to generate diversity is fundamental to the interaction of the virus with the host.

Despite a detailed knowledge of the molecular and structural biology of HCV, the pathogenesis of infection remains unclear. This is, at least in part, because there is no robust cell culture system for propagation of the virus or, despite recent advances, a widely accessible small animal model of HCV disease [7]. Many studies have addressed the role of individual virus proteins in transformed cell lines and in transgenic animals [7,8]. These studies have proved frustratingly inconclusive. For instance, HCV core protein can be shown to both sensitise and desensitise different (and sometimes the same) cell lines to apoptosis induced by a range of cytokines, and to either activate or inactivate cellular p53 and its regulatory pathway. Moreover, it causes tumours in some transgenic mouse models, but not in others [8]. The recent development of subgenomic 'replicons' has provided a system for stable high-level expression of virus RNAs and NS proteins [7]. This system, now permits production of structural proteins, but cannot couple RNA replication with virion assembly. Furthermore, it can be constructed with only a few virus isolates and cell lines, and is of limited utility in the study of virus–host interactions. Nonetheless, the replicon system represents a major advance. Equally encouraging is the drive to study the function of HCV proteins in primary cells in carefully selected animal models. An excellent study conducted in mice provided evidence that HCV core protein protects primary hepatocytes from apoptosis induced by cytokines expressed in the inflamed liver, thereby suggesting a mechanism for both virus persistence and the subsequent development of malignant disease [9].

EPIDEMIOLOGY

HCV is endemic in most parts of the world. There are, however, considerable temporal and geographical variations in the incidence and prevalence of infection. Age-specific analysis of prevalence has identified three broad patterns of transmission [1]. In the first of these, most HCV infections are found in individuals aged 30–49 years, indicating that the risk of transmission was greatest in the recent past and affected primarily young adults. This pattern predominates in the UK and the USA, where the principal risk factor for the transmission of HCV is known to be injecting drug use (IDU). In countries with

the second pattern, such as Japan, most infections are found in the elderly, consistent with the risk of HCV infection having been greater in the more distant past. In countries with the third pattern, such as Egypt, high rates of infection are observed in all age groups. In the two latter groups, contamination of equipment used to administer vaccines and unsafe healthcare procedures may be important means of transmission [1].

In contrast to the USA, where the National Health and Nutrition Examination Survey found that almost 2% of the population were HCV antibody-positive [2], no study of HCV in an unselected population has been performed in the UK. Estimates based on studies of low-risk groups, such as blood donors and antenatal women, suggest a prevalence of up to 0.5% in the general population. In contrast, a large study of injecting drug users in England and Wales found an overall prevalence of 30%, with rates of up to 70% in those who had injected over the longest period [3]. Risk factors for the acquisition of HCV in a UK regional population are listed in Table 1. This prospective study, incorporating five centres within the Trent region of England, found that HCV was most common among young adults, over half of whom had been born in the 1960s or later, and reported a male : female ratio of 2:1 [10]. This age and sex distribution is typical of injecting drug users, and the Trent study confirmed that IDU was the most common risk factor for infection. Approximately 50% of all infections were associated with HCV genotype 1, but a significant correlation was found between genotype 3 and infection by IDU. The second major risk factor for HCV in this study was receipt of blood components. The UK blood supply has, however, been screened for antibodies to HCV since 1993, and all blood components, other than those required for use within 24 h of collection, are now also screened for the presence of virus RNA. As a consequence, the risk of exposure to HCV through transfusion with blood or blood components in the UK is extremely low [11].

Table 1. Risk factors for hepatitis C virus infection among 769 patients in a cohort from a UK health region (data presented in part previously by The Trent HCV Study Group [10])

Risk factor	No. (%) of patients
Intravenous drug use	509 (66)
Receipt of blood components	132 (17)
Non-professional tattoo	18 (2.3)
Sex with drug user	13 (1.7)
Healthcare worker	12 (1.6)
Born outside the UK	23 (3)
Tattoos	13 (1.7)
Non-professional ear piercing	3 (0.4)
None of the above	46 (6)

In contrast to the clear and consistent evidence linking parenteral exposure and HCV infection, the role of sexual activity in spreading the virus remains controversial. Prevalence studies of the long-term sexual partners of patients with chronic HCV infection have found an average rate of infection of 1.5%, at least part of which may be explained by other shared risk behaviour [12]. A recent prospective study of 895 monogamous heterosexual partners of HCV-infected individuals followed for 10 years (providing a follow-up period of 8060 person-years) found no evidence of sexual transmission of this virus [13]. However, population-based studies have consistently shown an association between high-risk sexual behaviour and HCV infection [2,3], and this may be particularly true for HIV-infected men who have sex with men [14]. It is therefore likely that the nature of sexual activity, together with HIV coinfection, can increase the risk of sexual transmission of HCV. HIV may also affect the transfer of HCV from mother to child. The rate of vertical transmission of HCV in the absence of HIV infection is 6%, but is at least two-fold greater in infants born to HIV- and HCV-coinfected mothers [12]. Furthermore, while there is no consistent evidence that elective Caesarian section or avoidance of breast-feeding reduces transmission rates in mothers infected only with HCV, these measures appear to reduce the risk of transmission of HCV from coinfected mothers to infants [15].

DISEASE

The natural history of HCV infection remains surprisingly unclear. Large studies have suggested that up to 30% of infected individuals will develop cirrhosis, leading to end-stage liver failure and HCC [4,5]. There is, however, considerable variation in the rate of progression of HCV-associated liver fibrosis. Factors known to be associated with the presence of advanced liver disease on first biopsy are listed in Table 2. These risk factors, however, are derived largely from retrospective studies in which the dates of first infection for many of the study cohort are

Table 2. Factors established to predict the presence of advanced fibrosis on first liver biopsy in chronic hepatitis C virus infection [4,5,10]

Male sex
Duration of infection
Acquisition of infection at an age of > 40 years
High alcohol intake
Coinfection with hepatitis B virus

unknown. Recent prospective studies have addressed such limitations. The largest of these examined paired liver biopsies from 214 HCV-infected patients with predominantly mild disease [16], of whom 33% showed significant progression of fibrosis over a median period of 2.5 years. Independent predictors of progression on multivariant analysis were age at first biopsy, and the presence of fibrosis on first biopsy. Alcohol was not associated with fibrosis progression, but individuals who attend clinics for repeat liver biopsies are a selected group with a generally low alcohol intake. The overall fibrosis progression rate was 0.17 units/year, assessed according to the Ishak index of histological activity, indicating a mean time from infection to cirrhosis of about 35 years. These results are broadly comparable to those of other prospective studies [17,18], although necroinflammation [17] and interface hepatitis have also been found to predict the progression of fibrosis [18]. All of these results are consistent with the idea that hepatic inflammation is the substrate that drives fibrotic change. A further key conclusion arising from this work is that fibrosis progression is not linear, but accelerates with age, independent of the likely duration of infection. This may explain the relative absence of fibrotic liver disease in young women infected by contaminated gammaglobulin during pregnancy [19], and suggests that the number of HCV-infected patients with cirrhosis of the liver will rise as the study cohorts age.

Several studies have suggested that the presence of steatosis on liver biopsy correlates with the degree of fibrosis and the rate of disease progression [20,21]. Interpretation of these observations is complicated by the contribution of both virus and host factors, such as body mass index and alcohol consumption, to steatosis. Steatosis is more common following genotype 3 infection, and may represent a direct cytopathic effect of this virus [22]. Indeed, a multivariable logistic regression analysis of 755 patients with HCV infection found that steatosis was only predictive of disease progression in patients infected with genotype 3 [21]. The hypothesis that steatosis provides additional substrate for lipid peroxidation and amplifies hepatic inflammation in chronic HCV infection is attractive. Nonetheless, prospective studies have not found a correlation between disease progression and steatosis [16–18], and this remains an important area for further study.

The natural history of compensated virus cirrhosis has not been well-defined. A prospective study of 254 HCV-infected individuals with cirrhosis found that 30% developed at least one major complication during a median follow-up period of 93 months [23]. HCC was the most common complication, with a cumulative incidence of 28% at 10 years. Ascites, bleeding and encephalopathy were also reported. Death from liver disease occurred in 18% of the cohort, and the most frequent single cause was HCC. These results are broadly in accord with the largest previous European study [24], and demonstrate clearly that HCC is the most important complication of HCV-positive cirrhosis. This is consistent with the outcome of a very large historical cohort study which found that the relative risk of HCC in cirrhosis of virus aetiology was much higher than in cirrhosis associated with alcoholism (118.5 vs. 22.4) [25]. Once decompensation of HCV cirrhosis has occurred, the 5-year survival rate is *c.* 50%, with most deaths being liver-related [26,27].

In addition to causing chronic disease of the liver, HCV infection has been linked to extrahepatic disease. Indeed, more than 30 extrahepatic disease manifestations have been associated with HCV [27]. Most associations, however, have been claimed by studies that are either small or confounded by possible selection bias, and a clear role for the virus has not yet been established. In contrast, mixed cryoglobulinaemia is associated unequivocally with HCV infection. This may be a consequence of both general stimulation of the production of polyclonal rheumatoid factor by chronic virus infection, and the specific induction of monoclonal rheumatoid factor by HCV. More than 40% of individuals with chronic HCV infection have cryoglobulins in the peripheral blood, although only a minority develop features of systemic vasculitis [27]. It is striking that another potentially important extra-hepatic disease linked to HCV is also a product of aberrant B-cell regulation. Epidemiological studies from

Italy and Japan consistently show an increased prevalence of HCV in patients with non-Hodgkin's lymphoma of B-cell origin. However, similar studies from other parts of Europe and the USA have not confirmed this association, and a longitudinal study of 2162 HCV-infected individuals in Japan found a low incidence of non-Hodgkin's lymphoma of B-cell origin (reviewed in [27]). Furthermore, although the virus has a limited trophism for B-cells, HCV has not been found consistently in lymphoma cells *in vivo*, and no mechanism of lymphomagenesis in HCV infection has yet been described.

TREATMENT

Chronic hepatitis C virus infection

Monotherapy with interferon, the best available treatment for HCV infection for many years, produces a sustained response in <20% of patients. The introduction of combination therapy with interferon-α, injected subcutaneously three-times-weekly, and daily oral ribavirin was a major advance [28]. This regimen produced a sustained virus response (SVR), as defined by undetectable virus RNA in the peripheral blood at 24 weeks after stopping therapy, in *c.* 40% of previously untreated patients with chronic HCV infection. More recently, combination therapy using interferons modified by the addition of either a 12-kDa or a 40-kDa polyethylene glycol molecule (peginterferons) was found to be superior to combination therapy involving standard interferon or treatment with peginterferon alone [29,30]. Although the two forms of peginterferon are distinct pharmacologically, both are administered weekly and produce sustained and cumulatively higher levels in the blood than conventional three-times-weekly administration. In a trial of 1530 treatment-naïve patients with chronic HCV infection, 12-kDa peginterferon α-2b at a dose of 1.5 μg/kg plus ribavirin 800 mg produced an overall SVR of 54%. The SVR for genotype 1 was 42%, rising to *c.* 80% for genotype 2 or 3 infections [29]. In a similar, although better designed, trial, 40-kDa peginterferon α-2a at a dose of 180 μg plus ribavirin 1000 mg or 1200 mg (according to patient weight) achieved an overall SVR of 56% (46% for genotype 1) [30]. In both studies, a high virus load and the presence of severe fibrosis on liver biopsy correlated with a poor response to therapy. There was some evidence that the 40-kDa form was superior to the 12-kDa form in these hard-to-treat groups. The relative merits of the two available peginterferons are the subject of an ongoing comparative trial and will not be discussed further. It has been shown subsequently that genotype 2 and 3 disease can be treated with a 24-week course of peginterferon plus ribavirin, and that no additional benefit is gained by extending therapy to 48 weeks [31]. It has also become clear that the absence of at least a two-log drop in virus titre after 12 weeks of therapy has a powerful negative predictive value, and is an indication for stopping treatment in cases of genotype 1 disease [29–31]. In response to these results, the UK National Institute for Clinical Excellence has recommended that combination therapy with peginterferons should become the standard of care for the treatment of individuals aged >18 years with moderate-to-severe chronic HCV infection, defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation.

Despite these advances in the treatment of chronic HCV infection, there remains a pressing need for more effective therapies. Only *c.* 50% of individuals with genotype 1 disease will respond after combination therapy for 48 weeks. The reason for the consistently lower response rates of genotype 1 virus, in comparison to genotype 2 or 3, remains unclear. Response rates are likely to be even lower in men, or in those who have a high virus load or cirrhosis on liver biopsy, and may decrease further with increasing age [29,30]. In addition, there is evidence that African Americans with genotype 1 disease have lower response rates than Caucasian patients [32]. Conversely, the high response rates achieved following the treatment of patients with genotype 2 and 3 infection have prompted many hepatologists and infectious disease physicians to treat disease caused by genotypes 2 and 3 without performing a liver biopsy. This policy will result in the early treatment of many individuals with genotype 2 and 3 infection. The merits of such an approach will become clearer following completion of the UK Medical Research Council trial of early vs. late treatment for HCV infection. At the other end of the spectrum, the first analysis of the HALT-C trial [33], evaluating the effectiveness of treating previous non-responders, found that individuals

who failed to respond to standard interferon, given alone or as combination therapy, achieve an SVR of 18% when treated with peginterferon and ribavirin. Factors associated with an SVR were infection with genotype 2 or 3, previous interferon monotherapy, and lack of cirrhosis on liver biopsy.

Acute HCV infection

Acute infection with HCV is now an uncommon disease. Treatment of acute HCV infection, however, is a unique opportunity to prevent the evolution to chronic infection, particularly as several studies suggest that acute infection is very much more sensitive to therapy than established disease. The German Acute Hepatitis C Therapy Group treated 44 patients with interferon monotherapy during the acute phase of infection, and achieved a remarkable SVR of 98% [34]. A second German study treated only those patients who remained HCV RNA-positive at 3 months after the onset of hepatitis. This study achieved a comparable overall virus clearance of 91% in 60 patients, as a consequence either of spontaneous virus clearance or of treatment [35]. Interestingly, 52% of those with symptomatic disease cleared the virus, whereas all asymptomatic patients developed chronic infection before treatment. The most recent study, conducted in Japan, found that acute disease was exquisitely sensitive to interferon treatment lasting 4 weeks, but that delaying the initiation of treatment by 1 year reduced the response rate significantly [36]. These studies provide a rationale for the treatment of acute disease, although it may be reasonable to wait 3–6 months to allow symptomatic patients the chance to clear virus spontaneously. The reasons for the dramatic difference in the sensitivity to treatment of acute and chronic infection are unknown.

SPECIAL GROUPS

Healthcare workers

The prevalence of HCV infection in healthcare workers (HCWs) is comparable to that of the general population. Although the overall rate of HCV seroconversion following 'sharps' injury is *c*. 2% (range 0–10%) [12], the risk of a HCW transmitting the virus to a patient is very low in practice, even during exposure-prone procedures (EPPs). The policy of the UK Department of Health is that individuals engaged in EPPs who are found to be HCV RNA-positive must discontinue these activities. Furthermore, HCWs who plan a career involving EPPs, such as general surgery, must be screened and will not be permitted to proceed if found to be HCV RNA-positive. Practitioners already involved in EPPs are, however, not legally obliged to undergo screening for HCV. HCWs who have themselves been exposed to HCV by 'sharps' injury have been followed prospectively in the acute infection studies discussed in the previous section [34–36]. The data from these studies suggest that there is no rationale for post-exposure prophylaxis in a HCW exposed to HCV, but that individuals involved should be monitored carefully, and treatment reserved for those who seroconvert and fail to clear the virus.

HCV and HIV coinfection

The prevalence of coinfection with HCV and HIV has been reported to lie between 15% and 70%, with the highest prevalence in those individuals who acquired HIV by IDU [37,38]. The European Association for the Study of the Liver and the American Association for the Study of Liver Diseases both recommend that all HIV-positive individuals should be screened for HCV [37]. Coinfection with HIV affects all stages of HCV infection adversely. Indeed, end-stage liver disease associated with HCV infection is now one of the major causes of morbidity and mortality in HIV-infected individuals [37,38]. In contrast, the effect of HCV on progression and response to therapy of HIV disease remains unclear. It is, however, evident that infection with HCV is associated with a 2–10-fold increased risk of developing hepatoxicity in response to highly active anti-retroviral therapy (HAART) [37,38]. Early retrospective studies identified individual drugs, such as nevirapine, as particularly toxic in coinfected individuals, but evidence from prospective studies emphasises that HCV is an additional risk factor for hepatoxicity, irrespective of the HAART regimen used [38]. It is therefore of particular importance to monitor liver function tests meticulously in coinfected individuals receiving HAART. Moderate or severe liver damage, as defined by transaminase levels of up to

5–10-fold the normal upper limit (grade 3), usually resolves without any need to discontinue therapy, but a rise to >10-fold the normal upper limit (grade 4) is an indication to discontinue treatment. There is a theoretical risk that ribavirin may promote the mitochondrial toxicity syndrome associated with nucleoside reverse transcriptase inhibitors, and patients must be monitored at regular intervals for this complication [37,38]. Overall, however, >80% of coinfected individuals continue to benefit from HAART.

The first large randomised controlled trials of combination therapy with peginterferon in HCV- and HIV-coinfected individuals have now been published [39,40]. The results of the largest of these trials (APRICOT) [39] provide strong evidence that treatment with 40-kDa peginterferon α-2a and ribavirin for 12 months is effective in the treatment of coinfected individuals with stable disease and CD4 counts of >200/μL, or 100–200/μL with an HIV virus load of <5000 copies/mL. Furthermore, in the 286 subjects who received it, combination therapy for HCV did not appear to affect the control of HIV adversely, or to exacerbate the side-effects of HAART. Overall, SVRs were 40% (29% genotype 1) vs. 12% (7% genotype 1) for standard interferon and ribavirin, and 20% (14% genotype 1) for peginterferon alone. These results are encouraging, but drop-out rates were higher than for mono-infected individuals; indeed, 15% of patients failed to complete therapy for 48 weeks because of adverse events or laboratory abnormalities. It is also of note that coinfected patients may be at greater risk of hepatic decompensation, and those with a Child–Pugh score of six or greater should be treated with extreme caution. Nonetheless, the APRICOT trial and ACTG A5071 [40] provide a rationale for the use of combination therapy including the 40-kDa peginterferon for individuals with stable HIV disease who are coinfected with HCV.

Prisons

Most injecting drug users pass through the prison system at some time. It has been estimated that 30% of men who have injected drugs have done so in prison, and that 75% of those who inject in a prison environment share equipment [3]. The prison population is therefore at high risk of HCV infection, and transmission within prisons is known to occur. Estimates of seroprevalence vary according to the methods used to sample the population, but 37% of prisoners surveyed by unlinked anonymous testing were positive for HCV [41]. The 'Hepatitis C Strategy for England' [3] recognises prisons as a controlled environment in which treatment can be offered to a population with a high prevalence of both HCV infection and co-factors for disease progression, such as high alcohol consumption and coinfection with hepatitis B virus. It has, however, proved difficult to forge and maintain effective links between prisons and specialist hepatitis services. A thorough attempt to establish outreach clinics in a UK prison cluster proved effective in delivering health education, but had little effect on the identification or eradication of HCV in the prison population [41].

STRATEGIES FOR CONTROL OF HCV

Strategies for the prevention and control of HCV infection have been reviewed extensively [12] and are the main focus of the 'Hepatitis C Strategy for England' [3] and the follow-up document 'Hepatitis C Action Plan' [42]. These strategies arise from growing knowledge of the epidemiology of HCV and recognition of the efficacy of treatment in reducing the burden of disease in infected populations. They include the following:

- Intensified health promotion to discourage new IDU, including drugs education in schools.
- Prevention of infection in current injectors by provision of needle exchanges and harm reduction services.
- Increased professional and public awareness of HCV, with the particular aim of increasing the numbers of individuals tested for HCV infection.

Table 3. Suggested components of an ideal multidisciplinary clinical network for the management of hepatitis C infection in the UK (adapted from [3])

Specialist services for viral hepatitis, comprising:
Clinicians experienced in the diagnosis and management of viral hepatitis, including hepatologists and infectious disease physicians
Clinical nurse specialists
An accredited virology laboratory
Access to interventional radiology
Access to expert liver pathology
Other secondary care services, e.g., genitourinary medicine
Primary care
Drug and alcohol services
Prison medical services
Charities and voluntary groups

- Formation of multidisciplinary clinical networks to coordinate the care of HCV-positive patients and provide antiviral treatment according to National Institute for Clinical Excellence guidelines. The components of an ideal multidisciplinary clinical network are listed in Table 3.
- The creation of a coherent plan for the management of HCV in prisons.

Reduction in the incidence of new HCV infections and improved management of established infection, through multidisciplinary clinical networks or otherwise, are particularly critical if the predicted sustained increase in the number of patients with cirrhosis and HCC as a consequence of chronic HCV infection is to be reversed. A European study estimated that a 50% decline in the incidence of HCV from 1990 will still lead to an increase of 120–150% in HCV-related mortality in the course of the next 30 years [43]. In order to achieve a reduction in HCV-related mortality in this time period, new cases of HCV will need to be virtually eliminated [43]. Such dramatic changes will require a major revision of the current approach to the management of this important infection.

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